Amendments to the Claims

Please amend Claims 4-5, 11-17 and 39-46. The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing

Claim 1 (original): A method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor.

Claim 2 (original): The method of Claim 1 wherein the site is in need of a bone graft.

Claim 3 (original): The method of Claim 1 wherein the site is a segmental gap in a bone, a bone void or at a non-union fracture.

Claim 4: (currently amended): The method of Claim 1 wherein the agonist is a thrombin peptide derivative, or a physiologically functional equivalent thereof, comprising a polypeptide represented by the following structural formula ~~or a physiologically functional equivalent thereof~~:

Asp-Ala-R;

wherein R is a serine esterase conserved sequence.

Claim 5: (currently amended): The method of Claim 4 wherein the agonist ~~thrombin peptide derivative~~ consists of between about 12 and about 23 amino acids.

Claim 6 (withdrawn): The method of Claim 5 wherein the serine esterase conserved sequence consists of the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a *C*-terminal truncated fragment thereof having at least six amino acids, provided that zero, one, two or three amino acids in the

serine esterase conserved sequence differ from the corresponding position of SEQ ID NO 1.

Claim 7 (withdrawn): The method of Claim 5 wherein the serine esterase conserved sequence consists of the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a *C*-terminal truncated fragment thereof having at least nine amino acids, provided that zero, one or two of the amino acids in the serine esterase conserved region are conservative substitutions of the corresponding amino acid in SEQ ID NO 1.

Claim 8 (withdrawn): The method of Claim 5 wherein the serine esterase conserved sequence consists of the amino acid sequence of SEQ ID NO 2 (Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val, wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val), or a *C*-terminus truncated fragment of SEQ ID NO 2, said fragment having at least six amino acids.

Claim 9 (withdrawn): The method of Claim 8 wherein the thrombin peptide derivative comprises the amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO 3).

Claim 10 (withdrawn): The method of Claim 9 wherein the thrombin peptide derivative comprises the amino acid sequence Arg-Gly-Asp-Ala-Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val (SEQ ID NO 4), wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val.

Claim 11 (currently amended): The method of Claim 4 ~~Claim 10~~ wherein the agonist ~~thrombin peptide derivative~~ consists of the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- ~~(SEQ ID NO 5)~~ (SEQ ID NO.: 5), or an *N*-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the

agonist ~~thrombin peptide derivative~~ differ from the amino acid at the corresponding position of ~~SEQ ID NO 5~~ SEQ ID NO.: 5.

Claim 12 (currently amended): The method of Claim 4 ~~Claim 10~~ wherein the agonist ~~thrombin peptide derivative~~ consists of the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- ~~(SEQ ID NO 5)~~ (SEQ ID NO.: 5), or an *N*-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the agonist ~~thrombin peptide derivative~~ are conservative substitutions of the amino acid at the corresponding position of ~~SEQ ID NO 5~~ SEQ ID NO.: 5.

Claim 13 (currently amended): The method of Claim 5, wherein the ~~subject is administered a therapeutically effective amount of a physiologically equivalent~~ agonist comprises ~~thrombin derivative peptide comprising~~ a C-terminal amide.

Claim 14 (currently amended): The method of Claim 5, wherein the ~~subject is administered a therapeutically effective amount of a physiologically functional equivalent~~ agonist comprises ~~thrombin derivative peptide of the sequence Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-$CONH_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO.: 6).

Claim 15 (currently amended): The method of Claim 5, wherein the ~~subject is administered a therapeutically effective amount of a physiologically functional equivalent~~ agonist ~~thrombin derivative peptide comprising~~ comprises ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-$CONH_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO.: 6).

Claim 16 (currently amended): The method of Claim 5, wherein the ~~subject is administered a therapeutically effective amount of a physiologically functional equivalent~~ agonist ~~thrombin derivative peptide consisting~~ consists of ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH$_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO.: 6).

Claim 17 (currently amended): The method of Claim 11 wherein the agonist ~~thrombin peptide derivative~~ is administered in a pharmaceutical composition additionally comprising an implantable, biocompatible carrier.

Claim 18 (original): The method of Claim 13 wherein the implantable, biocompatible carrier is an osteoconductive matrix.

Claim 19 (original): The method of Claim 11 wherein the carrier comprises a polylactic acid/polyglycolic acid homopolymer or copolymer.

Claim 20 (withdrawn): The method of Claim 1 wherein the subject is a farm animal, a companion animal or a laboratory animal.

Claim 21 (withdrawn): A pharmaceutical composition comprising an implantable, biocompatible carrier and an agonist of the non-proteolytically activated thrombin receptor.

Claim 22 (withdrawn): The method of Claim 10 wherein the thrombin peptide derivative consists of the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID NO 5), or an *N*-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the thrombin peptide derivative are conservative substitutions of the amino acid at the corresponding position of SEQ ID NO 5.

Claim 23 (withdrawn): The pharmaceutical composition of Claim 21 wherein the thrombin receptor agonist is thrombin peptide derivative comprises a polypeptide represented by the following structural formula or a physiologically functional equivalent thereof:

Asp-Ala-R;

wherein R is a serine esterase conserved sequence.

Claim 24 (withdrawn): The pharmaceutical composition of Claim 22 wherein the carrier is a biodegradable synthetic polymer.

Claim 25 (withdrawn): The pharmaceutical composition of Claim 23 wherein the biodegradable synthetic polymer is a polylactic acid/polyglycolic acid homopolymer or copolymer.

Claim 26 (withdrawn): The pharmaceutical composition of Claim 22 wherein the carrier comprises collagen, fibrin, calcium phosphate salts, calcium sulfate, guanidine-extracted allogenic bone or a combination thereof.

Claim 27 (withdrawn): The pharmaceutical composition of Claim 22 wherein the carrier is injectable.

Claim 28 (withdrawn): The pharmaceutical composition of Claim 26 wherein the carrier is a poly(propylene fumarate) solution or a calcium phosphate ceramic paste.

Claim 29 (withdrawn): The pharmaceutical composition of Claim 22 wherein the pharmaceutical composition is administered as microparticles.

Claim 30 (withdrawn): The pharmaceutical composition of Claim 22 wherein the thrombin peptide derivative consists of between about 12 and about 23 amino acids.

Claim 31 (withdrawn): The pharmaceutical composition of Claim 30 wherein the serine esterase conserved sequence consists of the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a *C*-terminal truncated fragment thereof having at least six amino acids, provided that zero, one, two or three amino acids in the serine esterase conserved sequence differ from the corresponding position of SEQ ID NO 1.

Claim 32 (withdrawn): The pharmaceutical composition of Claim 30 wherein the serine esterase conserved sequence consists of the amino acid sequence of SEQ ID NO. 1 (Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val), or a *C*-terminal truncated fragment thereof having at least nine amino acids, provided that zero, one or two of the amino acids in the serine esterase conserved sequence are conservative substitutions of the corresponding amino acid in SEQ ID NO 1.

Claim 33 (withdrawn): The pharmaceutical composition of Claim 30 wherein the serine esterase conserved sequence consists of the amino acid sequence of SEQ ID NO 2 (Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val), wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val), or a *C*-terminus truncated fragment of SEQ ID NO 2, said fragment having at least six amino acids.

Claim 34 (withdrawn): The pharmaceutical composition of Claim 30 wherein the serine esterase conserved sequence has the amino acid sequence of SEQ ID NO 2 (Cys-X_1-Gly-Asp-Ser-Gly-Gly-Pro-X_2-Val), wherein X_1 is Glu or Gln and X_2 is Phe, Met, Leu, His or Val), or a *C*-terminus truncated fragment of SEQ ID NO 2, said fragment having at least six amino acids.

Claim 35 (withdrawn): The pharmaceutical composition of Claim 30 wherein the thrombin peptide derivative comprises the amino acid sequence Arg-Gly-Asp-Ala (SEQ ID NO 3).

Claim 36 (withdrawn): The pharmaceutical composition of Claim 35 wherein the thrombin peptide derivative consists of the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID NO 5), or an *N*-terminal truncated fragment thereof, provided that zero, one, two or three amino acids at positions 1-9 in the thrombin peptide derivative differ from the amino acid at the corresponding position of SEQ ID NO 5.

Claim 37 (withdrawn): The pharmaceutical composition of Claim 35 wherein the thrombin peptide derivative consists of the amino acid sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val- (SEQ ID NO 5), or an *N*-terminal truncated fragment thereof, provided that zero, one or two amino acids at positions 1-9 in the thrombin peptide derivative are conservative substitutions of the amino acid at the corresponding position of SEQ ID NO 5.

Claim 38 (withdrawn): The pharmaceutical composition of Claim 30 comprising a physiologically equivalent thrombin derivative peptide, wherein the physiologically equivalent thrombin derivative peptide comprises a C-terminal amide.

Claim 39 (withdrawn - currently amended): The pharmaceutical composition of Claim 30 comprising a physiologically equivalent thrombin derivative peptide, wherein the physiologically functional equivalent thrombin derivative peptide comprises ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH$_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH$_2$ (SEQ ID NO.: 6).

Claim 40 (withdrawn - currently amended): The pharmaceutical composition of Claim 30 comprising a physiologically functional equivalent thrombin derivative peptide,

wherein the physiologically functional equivalent thrombin derivative peptide consists of ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-CONH$_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH$_2$ (SEQ ID NO.: 6).

Claim 41 (currently amended): A method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor, said agonist consisting of ~~a peptide having~~ the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val ~~(SEQ ID NO 5)~~ (SEQ ID NO.: 5).

Claim 42 (currently amended): A method of stimulating bone growth at a site in need of a bone graft in a subject, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor, said agonist consisting of ~~a peptide having~~ the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val ~~(SEQ ID NO 5)~~ (SEQ ID NO.: 5).

Claim 43 (currently amended): A method of stimulating bone growth in a subject at a segmental bone gap, a bone void or a non-union fracture, said method comprising the step of administering to the bone gap, bone void or nonunion fracture, a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor, said agonist consisting of ~~a peptide having~~ the sequence Ala-Gly-Try-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val ~~(SEQ ID NO 5)~~ (SEQ ID NO.: 5).

Claim 44 (currently amended): A method of stimulating bone growth at a site in need of osteoinduction, said method comprising the step of administering to the site a

therapeutically effective amount of ~~a physiologically functional equivalent~~ an agonist of the non-proteolytically activated thrombin receptor, said agonist ~~thrombin derivative peptide~~ consisting of the sequence of ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-$CONH_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO.: 6).

Claim 45 (currently amended): A method of stimulating bone growth at a site in need of a bone graft in a subject, said method comprising the step of administering to the site a therapeutically effective amount of ~~a physiologically functional equivalent~~ an agonist of the non-proteolytically activated thrombin receptor, said agonist ~~thrombin derivative peptide~~ consisting of the sequence of ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-$CONH_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO.: 6).

Claim 46 (currently amended): A method of stimulating bone growth at a segmental bone gap, a bone void or a non-union fracture, said method comprising the step of administering to the bone gap, bone void or non-union fracture a therapeutically effective amount of ~~a physiologically functional equivalent~~ an agonist of the non-proteolytically activated thrombin receptor, said agonist ~~thrombin derivative peptide~~ consisting of the sequence of ~~Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-$CONH_2$ (SEQ ID NO: 6)~~ Ala-Gly-Tyr-Lys-Pro-Asp-Glu-Gly-Lys-Arg-Gly-Asp-Ala-Cys-Glu-Gly-Asp-Ser-Gly-Gly-Pro-Phe-Val-NH_2 (SEQ ID NO.: 6).